Title: How robust are clinical trials in heart failure?

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Abstract

Aims: Guidelines for the management of chronic heart failure (CHF) cite the results of randomized controlled trials (RCTs) to support treatment recommendations. The significance of an observed treatment-effect relies on the use of a boundary p-value, most commonly $p<0.05$. There is concern about relying on arbitrary threshold p-values to report results as "statistically significant". The "fragility index" (FI) has been proposed as an additional measure of the robustness of trial findings. FI is the minimum number of events needing to change from a non-event to an event in order to render a significant result non-significant. We calculated the FI to examine the robustness of statistically significant RCTs in CHF.

Methods and results: Two reviewers extracted data from RCTs supporting treatment recommendations in CHF guidelines. 25 eligible trials were identified with a median sample size of 2331 patients (range 129-8399) and a median number of primary endpoints of 688.5 (range 88-2031). For the primary endpoint (analysed for 20 trials), the median FI was 26 (range 0-118). The FI was d10 in 7 (35%) of these 20 trials, and in 4 (20%) trials the number of patients lost to follow-up in the treatment group exceeded the FI.

Conclusion: The results of some large RCTs in CHF hinge on a small number of events. The FI offers an additional, easy to understand metric, which augments the standard reporting of boundary p-values for statistical significance. The FI helps in the interpretation of the robustness of the results of RCTs.

Keywords: Heart failure; Clinical trials

INTRODUCTION

The practise of evidence-based medicine emphasises the importance of the results of randomised control trials (RCTs) in guiding and justifying treatment decisions.[1] It is therefore crucial that such results are robust and that guideline writers and practitioners have a clinically meaningful and readily understandable method of evaluating robustness. Many clinicians, however, focus on relative risk reductions derived from hazard ratios, the 95% confidence intervals around these, and the threshold p-value of <0.05 which is commonly taken to denote statistical significance.[2] However, reliance on these metrics alone is of concern.[3] Implicit in the reporting of a relative risk reduction as "significant" is the assumption that a true treatment effect exists. Sample size, number of events, number of patients lost to follow-up, along with other factors including whether there is more than one trial, are also important determinants of the robustness of the findings.[4,5]

In order to assist the interpretation of trials an additional statistical metric, the "fragility index" (FI), has been proposed as a tool to evaluate the robustness of results.[6] FI is the minimum number of events that need to change from a non-event to an event in order to render a significant result non-significant. The smaller the index, the more fragile the result. The principle underlying FI can be illustrated using an example of a trial with 100 patients randomised equally to treatment or placebo. If 10 patients in the treatment group experience an event, compared with 20 patients in the placebo group, the resultant p-value is 0.049 using a two-sided Fisher's exact test. If only one more event is added to the treatment group (n=11) while maintaining the same event rate in the placebo group, the trial loses "significance" as the p-value increases to 0.083.

To explore the value of FI, we examined its use in assessing the robustness of the results of trials in chronic heart failure (HF) with reduced rejection fraction (HF-REF) as this is one of the most evidence-based areas in the whole of medicine.[7,8] Multiple RCTs involving tens of thousands of patients have evaluated the effects of pharmacological and non-pharmacological therapies over the past thirty years. We analysed the trials providing the basis of guideline-recommended therapy in this condition. We also tested the value of three extensions of the FI concept. Firstly, we examined the FI for the different regulatory p-value thresholds for approval of a treatment based upon two independent trials compared with one single trial. Secondly, we studied the impact of loss to follow-up for vital status on the fragility of results. Finally, we explored the concept of FI applied to the results of a group of neutral trials in HF-REF.

METHODS

We reviewed published guidelines for chronic HF-REF. We identified trials used to support recommendations for pharmacological or non-pharmacological treatments. We calculated the FI for the reported outcomes in these trials. We also explored the relationships between trial characteristics and the fragility of the primary outcome.

Identification of studies

We searched the electronic databases Medline and Embase using the terms “heart failure”, “management” and “guidelines” as title or keywords published in English after January 2010. Guidelines and their most recent updates from 5 international bodies were identified.[7–11] These were examined to identify RCTs used to support the treatments in management algorithms for patients with HF-REF. Positive RCTs published since guideline publication were included by consensus of the authors.

Two reviewers (KD and RC) independently reviewed all identified abstracts. Trials were included if they reported at least one statistically significant dichotomous primary or secondary outcome ($p<0.05$ or a 95% confidence interval that excluded the null value) and randomised patients to treatment or control in a 1:1 design. The FI is not suitable for use in situations where the ratio of intervention to control subjects is not 1:1 as altering the number of events in the control or intervention arm will lead to different results for the FI.[6,12,13]

Data analysed

Two reviewers independently screened the abstracts and full publications of included trials. They used a standard table to extract data from the trial and a third reviewer resolved any discrepancy. Data recorded included details of the primary outcome (sample size; event

numbers; whether outcome was composite; and number lost to follow-up). We also recorded, where available, the details for the following additional outcomes: all-cause mortality, cardiovascular mortality and HF hospitalisation. If data were not available in the primary or subsequent trial publications this information was then sought through correspondence with trial authors or from publically available Food and Drug association (FDA) documentation.

FI calculation

Using the method described by Walsh et al. FI for the statistically significant primary and secondary outcomes were calculated.[6] We recorded the results for each outcome in a two-by-two contingency table. We calculated the p-value for each outcome using the two-sided Fisher's exact test. One event at a time was iteratively added to the group with smaller number of events (while subtracting one patient from the group with no events to maintain the total number of patients constant) and the p-value for the two-by-two table calculated. The FI for an outcome was the smallest number of added events required to result in a p-value of 0.05 or greater (Supplementary Figure 1).

Statistical analysis

We report normally distributed and skewed continuous variables as means with standard deviations and medians with interquartile ranges (IQRs), respectively. We tested between group differences for significance using a Mann-Whitney U-Test for non-parametric data. Two-sided significance testing was used and a p value <0.05 was considered significant. All analyses were performed using Microsoft Excel (Microsoft, Santa Rosa, CA, USA; 2015) and SPSS version 22 (IBM, Chicago, IL, USA; 2013). Correlations between FI and treatment effect-size, sample-size and number of events were calculated using the Spearman rank test for non-normal data. We also calculated the FI for two value thresholds: $p<0.05$ (which is

sufficient for regulatory approval when obtained in each of two independent trials) and for $p<0.00125$ (the p value required for regulatory approval if only one trial is submitted). Additionally, because loss to follow-up for vital status can reduce the integrity of a trial, we compared FI to the number lost to follow-up. The number of patients lost to follow-up included, where published, the number reported as having "withdrawn consent" because, in many jurisdictions, this means that follow-up for vital status is not permitted. Finally, we extended the concept of FI to neutral trials (those with $p\geq0.05$) of treatments not advocated in the treatment of HF-REF. FI was calculated by subtracting events from the investigational treatment group (adding non-events to this group to keep number of patients constant) and calculating the Fisher's exact p-value. The FI was the number of events required to result in $p<0.05$ (in other words, the outcome resulting in the investigational treatment demonstrating a statistically significant benefit).

RESULTS

Trial selection

Five international guidelines on the management of chronic HF were identified and the most recent updates reviewed.[7–11] We identified 29 trials used to support the recommendation of a treatment in patients with HF-REF. One trial did not require or report ejection fraction and two others included patients with both HF-REF and HF with preserved ejection fraction).[14–16] Among these 29 trials, 25 met the inclusion criteria (Supplementary data -Table 1).[14–45] We excluded 4 trials because they did not allocate patients to treatment or comparator in a 1:1 ratio.[46–49]

Trial characteristics

Table 1 summarises the characteristics of the 25 reviewed trials. The median sample size was 2331 (range: 129-8399). The median follow-up in months was 25.5 (6.3-58). The number of trials stopped early was 8 (32%). Of the 25 trials examined, 20 (80%) were placebo-controlled, 3 (12%) had an active comparator design, and 2 (8%) were dose comparison trials.

Data were available for the three additional outcomes of interest (all-cause mortality, cardiovascular mortality and HF hospitalisation) in 21 (84%) trials. Information for one or two of these additional endpoints was missing in 3 (15%) and 1 (5%) trials, respectively.

The effect of the investigational treatment on the primary endpoint was significant in 23 (92%) trials. Two trials (A-HeFT and IN-TIME) had significant composite score primary endpoints (non-dichotomous), meaning no FI was calculable (the dichotomous secondary endpoints were included in the analysis).[34,44] Another trial (CHAMPION) used the primary

endpoint of total number of HF hospitalisations which was not suitable for calculation of the FI (it did however have a secondary endpoint of number of patients hospitalised with HF which was included).[16] Therefore, we calculated FI for the primary outcome in 20 trials. The median number of patients with a primary outcome was 688.5 (range: 88-2031). The primary outcome was a composite in 11 (55%) of these trials. Reported p values for the primary outcome were less than 0.05 but greater than or equal to 0.01 in 4 (20%) trials, less than 0.01 but greater than or equal to 0.001 in 7 (35%), and less than 0.001 in 9 (45%). The effect of treatment on the additional endpoints of all-cause mortality, cardiovascular mortality and HF hospitalisation was significant in 16,16 and 18 trials respectively (not necessarily the same trials) and the median numbers of patients with these outcomes were 384 (range: 37-1546), 321.5 (29-1251) and 504.5 (134-2090), respectively.

Fragility index

Tables 2 and 3 summarises FI for the examined endpoints and according to different trial characteristics. The median FI for the primary endpoint in the 20 trials analysed was 26 (Interquartile range [IQR]: 8.5-39.25, range: 0-118) [Table 3]. One trial had a FI of 0 (Table 3).[45] This trial was originally significant only after adjustment for predictors of the primary endpoint. The FI for trials with a composite outcome and those with a single primary endpoint was similar. The median FI for all-cause mortality, cardiovascular mortality and HF hospitalisation was 13.5 (IQR: 5-33.75; range: 0-54), 9.5 (3-34; 3-34) and 38.5 (19.5-55.25; 2-191), respectively. The FI was higher in trials stopped early (median: 37, IQR: 30-61) than in those not stopped prematurely (median: 17, IQR: 6-31).

Correlation between FI and sample-size, number of events, treatment effect-size and p-value

FI was not significantly correlated with total sample size (R=0.312, p=0.18) or number of patients experiencing the primary endpoint (R=0.007, p=0.977) [Figure 1A and 1B]. There was no correlation between FI and the treatment/comparator hazard ratio (expressed as a relative risk reduction) for the primary endpoint or any of the other endpoints examined (Figure 2A-D).

FI for p-value thresholds of <0.05 and <0.00125

We calculated FI for p<0.05 (sufficient for regulatory approval when obtained in each of two separate trials) and for p<0.00125 (the p-value required for regulatory approval when a single trial is submitted). Of the 20 trials analysed, only 10 (50%) had a FI of >0 when considering the lower p-value (single trial) threshold (Table 4). The median FI for these 10 trials was 18 (IQR: 7.5-30, range: 2-68).

FI compared with number lost to follow-up for vital status

The number of patients lost to follow-up was available for all trials and was ≥1% of total sample size in 7 (35%) of the 25 trials examined in which the FI was calculated for the primary endpoint. The total number lost to follow-up in the treatment group was the same as or greater than the FI for the primary endpoint in 4 (20%) trials. These trials, their respective number lost to follow-up in the treatment group and FI for the primary endpoint were HEAAL (41 and 4), SENIORS (16 and 2), SHIFT (75 and 67), and HF-ACTION (59 and 0).[15,24,36,45]

FI for neutral trials (p≥0.05)

Supplementary table 2 summarises the details of 20 notable neutral trials in patients with HF-REF where the investigational treatment was not shown to be beneficial for the primary endpoint (p≥0.05).[50–69] The median FI for the primary endpoint was 30 (IQR: 14.75-52.25, range: 5-74).

DISCUSSION

We examined the robustness of the results of the trials supporting treatment recommendations in international HF-REF guidelines. The median FI for the primary endpoint in these trials was 26 (i.e. on average, 26 additional events were required to change a result from significant to non-significant). This compares favourably with the median of 8 found by Walsh and colleagues in their original analysis of nearly 400 trials covering a spectrum of medical and surgical interventions.[6] Indeed, in that previous study, 25% of trials had a FI of d3.

The lack of correlation between the treatment effect-size for the primary endpoint and FI illustrates how the result most practitioners focus on is an unreliable guide to the robustness of trial findings. Similarly, there was a lack of correlation between FI and either number of patients randomized or the number of patients experiencing a primary endpoint.

The recently published statement by the American Statistical Association regarding p-values has highlighted the issues surrounding the common reliance on the use of boundary p-values (most commonly <0.05) to infer statistical significance and the potential size of a treatment effect.[3] An important principle stresses is that a p-value, or statistical significance, does not measure the size of an effect or the importance of a result.

Most clinical trials are designed on the basis of event-rates and sample sizes large enough to accrue an adequate number of events to provide sufficient power to allow robust assessment of the treatment effect. Despite this, as we have shown, the FI varies widely among trials. This variation reflects a number of factors including the anticipated treatment effect-size, event rates and the power of the study (e.g. 80% or 90%). Although early stopping for

efficacy might in theory lead to a small FI, we found FI was actually higher in those trials, presumably reflecting the stringent stopping rules employed and the rarity of very early termination.

Based on the strength, depth and breadth of evidence available, international guidelines for HF-REF give the strongest recommendation (i.e. class 1, level A) to five treatments: angiotensin-converting enzyme inhibitors (ACE-I), beta-blockers, mineralocorticoid receptor antagonists (MRA), implantable cardioverter-defibrillators (ICD), and cardiac resynchronization therapy (CRT).[7–11] The three cornerstones of pharmacological therapy, ACE-Is, beta-blockers, and MRAs, had median FI of 8.5, 33 and 57.5, respectively, based on the primary endpoints in the relevant trials. However, the primary endpoint contributing to each of these estimates differed among trials, making direct comparison difficult. This is best illustrated by the two pivotal MRA trials, RALES and EMPHASIS-HF, in which FI for the primary endpoint was 54 and 61, respectively.[32,33] However, for all-cause mortality FI was 54 and 5, respectively (all-cause mortality was the primary endpoint in RALES whereas the composite of cardiovascular death or HF hospitalisation was in EMPHASIS-HF). This illustrates the importance of "like-with-like" comparisons when examining endpoints across trials, which we believe is the most appropriate way to compare outcomes. The difference observed probably reflects the smaller number of deaths in EMPHASIS-HF compared with RALES due to the different patients enrolled, the different eras in which these two trials were conducted (RALES preceded use of beta-blockers and devices) and the premature termination of EMPHASIS-HF. Both trials, however, showed a robust treatment effect on HF hospitalisation (FI 41 and 49, respectively). Of course, it is also important that there are *two* large trials with a MRA in chronic HF-REF and a supporting trial in patients with left

ventricular systolic dysfunction (LVSD) and HF (or diabetes mellitus) after myocardial infarction (MI).[70]

The relatively lower FI for ACE-Is is of interest given that these are the longest-standing evidence-based treatment in HF-REF. The two trials supporting the use of ACE-I, CONSENSUS and SOLVD-T, had a FI for the primary endpoint (all-cause mortality) of 7 and 10, respectively.[14,17] The low FI in CONSENSUS is due to few deaths, related to the small sample size (n=253) and premature trial termination. However, SOLVD-T was 10 times as large and accrued 8 times as many deaths but still had a modest FI for all-cause mortality. The effect of enalapril on HF hospitalisation in SOLVD-T was, by comparison, very robust, with a FI of 91. Also, as with MRAs, any concern about robustness is further alleviated by having supporting trials in patients LVSD, HF or both after MI, as well as a trial in patients with chronic asymptomatic LVSD.[71–74]

Of the current key pharmacological interventions, beta-blockers had the most consistent and robust effect on all-cause mortality with three placebo-controlled trials and one active-controlled trial with FI of over 30 for all-cause mortality and similarly large FI for HF hospitalisation. One trial in much older patients, not all of which had HF-REF, did not show a reduction in mortality. While this difference may reflect the patients enrolled, it is also possible that the beta-blocker studied was less effective.[75]

The two CRT trials with 1:1 randomization, CARE-HF and RAFT, each had a robust FI for the primary endpoint (40 and 23, respectively), as well as for mortality and HF hospitalization and are supported by two other trials without 1:1 randomization.[40,41,47,48]

The largest FI (118) for any primary endpoint was obtained in PARADIGM-HF which compared the angiotensin neprilysin inhibitor sacubitril/valsartan to enalapril.[37] This trial also had one of the highest FI for all-cause mortality, at 49 (second only to RALES). PARADIGM-HF also highlights an extension to the basic FI metric that might be added in future analyses. Unlike the other drugs discussed above, there is only *one* trial supporting the use of sacubitril/valsartan. An additional measure that could be included in this situation is calculation of the FI not only for $p<0.05$ (sufficient for regulatory approval when obtained in each of two separate trials) but also for $p<0.00125$ (the p value required for regulatory approval if only one trial is available). Using this criterion, FI for the primary endpoint fell to 68 in PARADIGM-HF. When the same approach was applied to SHIFT, FI also remained relatively robust (22).[36] However, in REMATCH (a controlled trial of a first-generation left ventricular assist device) FI fell to 3 and in SCD-HeFT (the only trial of an ICD in patients with chronic HF-REF), the FI fell to zero.[38,42] In other single trials, neither digoxin nor exercise prescription improved the primary outcome.[35,45] In the trials using the combination of hydralazine and isosorbide dinitrate, the primary outcome was not dichotomous in one and the other had a FI of zero.[34,46] There is also uncertainty about the robustness of the benefit of remote monitoring interventions.[16,44]

Another extension of the basic FI calculation we recommend is comparison with the number of patients lost to follow-up for vital status. The total number of patients lost to follow-up for vital status in the treatment arm was greater than FI in 4 trials. The implication of this is similar to the "worst case scenario" sometimes used by regulatory agencies in which all patients lost in the placebo group are considered alive and those lost in the active therapy group considered dead. As a result, even if a trial has a large FI, the results may not be as robust as they might seem. Take for example SHIFT, which had a FI of 67 for the primary

outcome, although no significant effect on cardiovascular or all-cause mortality. Assuming withdrawal-of-consent equated to lost to follow-up for vital status, then 75 patients in the ivabradine group would have missing vital status, a number considerably larger than FI.

The extension of the concept of FI to neutral trials is also of interest as, in the same way, a large FI provides assurance about the robustness of the results i.e. that the neutral outcome is likely to be true rather than due to deficiencies in trial design or conduct e.g. inadequate power, too few events, an anticipated treatment effect that was optimistically large etc. Our analysis of 20 trials showed that the median FI was 30, suggesting that the majority of neutral trials examined can be considered to be robust. The one exception was STICH, a trial with a FI of 5 (the lowest of all the neutral trials) which investigated the effect of coronary-artery bypass grafting (CABG) in addition to medical therapy in patients with HF-REF and coronary artery disease.[50] This means that 5 fewer deaths in the CABG arm of the trial would have resulted in a statistically significant result (measured by Fisher's exact test). This may be a particular issue in surgical trials where there is always a small initial excess of deaths in the active intervention arm, with later "catch-up" if the surgery is beneficial. In keeping with this, the recently published 10-year extended follow-up of this trial demonstrated a significantly lower mortality in the CABG group compared with the medical therapy group.[76] This illustrates the potential value of extended follow-up in surgical (and potentially other) trials provided the number of patients lost to follow-up of vital status is kept low.

Our analysis has limitations. The concept of FI can only be applied to dichotomous endpoints although the majority of RCTs supporting guidelines are likely to be based on dichotomous endpoints. Walsh et al. found no material difference in the FI between time-to-event data and frequency data, which they considered consistent with the concept that most results are

sensitive to the number of events in each group rather than the timing of the events.[6] Nevertheless, there may still be a concern about applying the FI to time-to-event data where the numbers of events in both groups are similar but there is a clear difference in the timing of the events. This could result in the inappropriate conclusion that such trials are excessively fragile. We have also mitigated this concern for composite time-to-event endpoints by calculating the FI for the individual components (all-cause mortality, cardiovascular mortality and HF hospitalisation) of these endpoints. We examined a moderate number of trials, therefore our ability to draw inference regarding the relationship between trial characteristics and FI is limited. Certain treatments were not as well represented as others, in particular devices, due to the majority of trials not using 1:1 randomisation. Because trials are powered to detect the presence of a treatment effect for the primary endpoint, interpretation of the fragility of secondary endpoints may be limited.

Conclusion

The FI offers an additional and easy to understand metric to the standard reporting of hazard ratios, 95% confidence intervals and boundary p-values for statistical significance in the interpretation of the robustness of RCTs. FI aids interpretation of the findings of randomized controlled trials. When applied to the evidence used to support guideline recommended treatments in HF-REF, we found that the significance of 7 of 20 trials (35%) rested on 10 or fewer events. However, the majority of treatments with the highest level of guideline recommendation were the more robust of the trials examined.

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Conflict of interest

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Figure Legend

Figure 1A - Relationship between the fragility index and the total sample size

Figure 1B - Relationship between the fragility index and the total number of primary outcome events

Figure 2A - Relationship between the fragility index and the relative risk reduction for the primary endpoint

Figure 2B - Relationship between the fragility index and the relative risk reduction for all-cause mortality

Figure 2C - Relationship the fragility index and the relative risk reduction for cardiovascular mortality

Figure 2D - Relationship between the fragility index and the relative risk reduction for heart failure hospitalisation

Figure 1

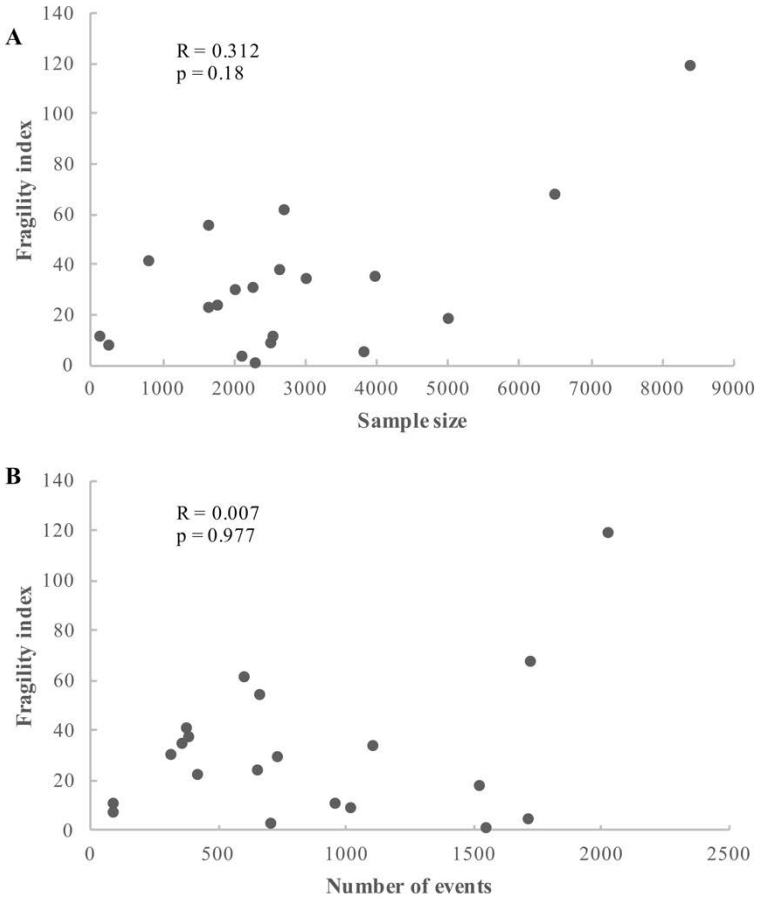

Figure 1
A - Relationship between the fragility index and the total sample size
B - Relationship between the fragility index and the total number of primary outcome events

Figure 2

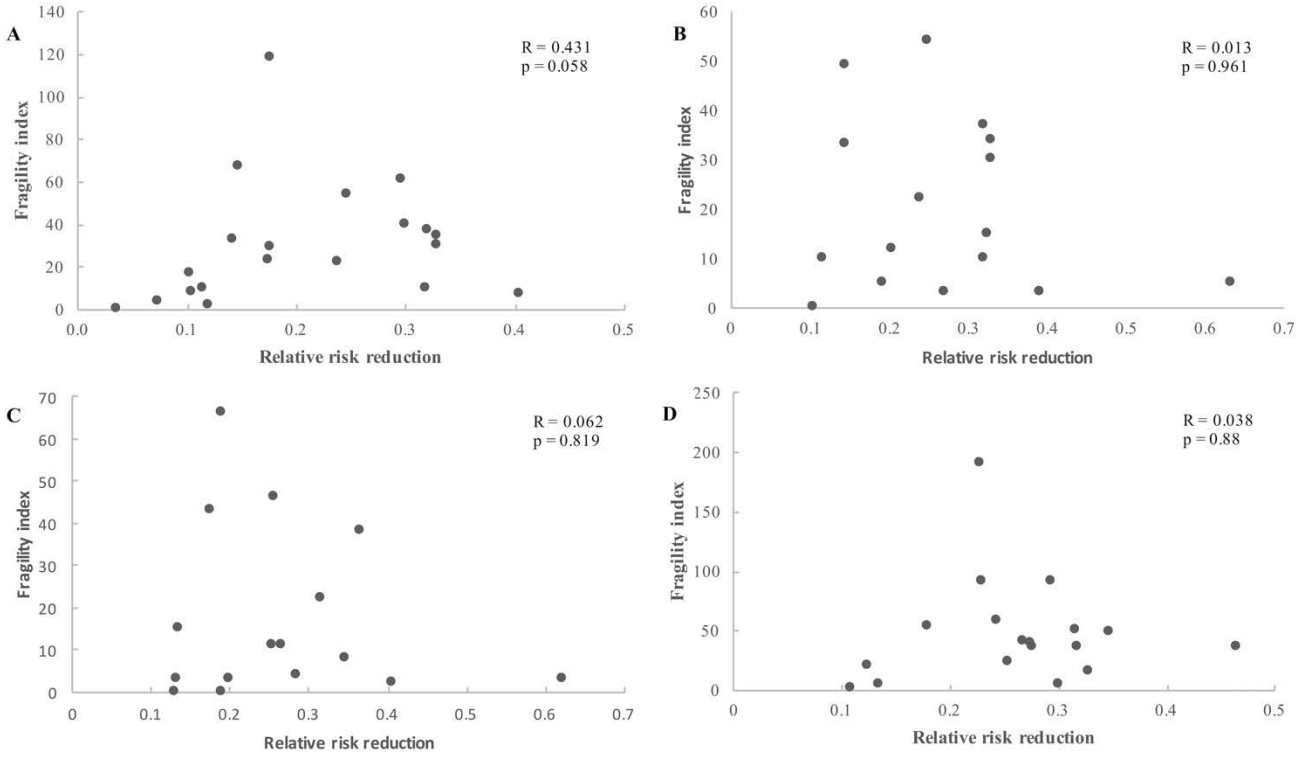

Figure 2

A- Relationship between the fragility index and the relative risk reduction for the primary endpoint
B - Relationship between the fragility index and the relative risk reduction for all-cause mortality
C - Relationship the fragility index and the relative risk reduction for cardiovascular mortality
D - Relationship between the fragility index and the relative risk reduction for heart failure hospitalisation

Table 1: Characteristics of included trials

Trial Characteristic	Number (n= 25)*****
Sample size, median (min-max)	2331 (129-8399)
Follow up (months), median (min-max)	25.5 (6.3-58)
Stopped Early	8 (32)
Placebo controlled	20 (80)
Active comparator	3 (12)
Dose Comparison	2 (8)
Primary endpoint	
Reported p-value < 0.05*§*	20 (80)
<0.05-0.01	4 (20)
<0.01-0.001	7 (35)
<0.001	9 (45)
Number of outcome events, median (min-max)	688.5 (88-2031)
Composite outcome	11 (55)
Secondary endpoint	
All cause mortality	
Reported p-value < 0.05	16 (64)
Number of outcome events, median (min-max)	384 (37-1546)
Cardiovascular mortality	
Reported p-value < 0.05	16 (64)
Number of outcome events, median (min-max)	321.5 (29-1251)
Heart failure hospitalisation	
Reported p-value < 0.05	18 (72)
Number of outcome events, median (min-max)	504.5 (134-2090)

* n (%) unless otherwise stated

§ 3 trials had a significant primary endpoint but were excluded from fragility index analysis due to a non-dichotomous endpoint (A-HeFT and IN-TIME[34,44]) and an endpoint of total heart failure hospitalisations (CHAMPION[16])

*Abbreviations**:*** min, minimum; max, maximum; n, number.

Table 2: Fragility index for outcomes and subgroups of trial characteristics

Trial Characteristic	Median Fragility Index (IQR)
Primary endpoint (n=20)	26 (8.5-39.25)
Composite (n=11)	23 (4-61)
Not composite (n=9)	30 (10-35)
Secondary endpoints	
All-cause mortality (n=16)	13.5 (5-33.75)
Cardiovascular mortality (n=16)	9.5 (3-34)
Heart failure hospitalisation (n=18)	38.5 (19.5-55.25)
Early stopping	
Stopped early (n=7)	37 (30-61)
Not stopped early (n=13)	17 (6-31)
Trial design	
Placebo controlled (n=16)	25.5 (8.5-39.25)
Active comparator (n=3)	33
Dose Comparison (n=1)	4
Sample Size	
129-1676 (n=5)	22 (8.5-47)
1677-2331 (n=5)	23 (1-29.5)
2332-3029 (n=5)	33 (9-49)
3030-8399 (n=5)	34 (10.5-92.5)
Number of primary endpoint events	
88-383 (n=5)	30 (8.5-37)
384-670 (n=5)	37 (22.5-57.5)
671-1112 (n=5)	10 (5-31)
1113-2031 (n=5)	17 (2-92.5)

Abbreviations: IQR, interquartile range; n, number.

Table 3: Fragility index for the primary and secondary outcomes

Trial	Primary Endpoint	Fragility Index			
		Primary Endpoint	All-Cause Mortality	CV Mortality	HF Hospitalisation
ACE- i					
CONSENSUS[14]	All cause mortality at 6 months	7*	3*	4	-
SOLVD-Treatment[17]	All cause mortality	10	10	15	91
ATLAS[18,19]	All cause mortality	NS	NS	NS	21
ARB					
Val-HeFT[20,21]	All cause mortality/ HF hospitalisation/ resuscitated cardiac arrest/administration of IV inotropic or vasodilator drugs for 4 or more hours.	17	NS	NS	59
CHARM-Alternative[22]	CV death/ HF hospitalisation	29	0¶	0¶	40
CHARM-Added[23]	CV death/ HF hospitalisation	8	NS	3	5
HEAAL[24]	All cause mortality/HF hospitalisation	4	NS	NS	2
² -Blockers					
CIBIS II[25]	All cause mortality	37	37	11	37
MERIT-HF[26,27]	All cause mortality	34	34	38	50
COPERNICUS[28,29]	All cause mortality	30	30	22	37
COMET[30,31]	All cause mortality	33	33	43	NS
SENIORS[15]	All cause mortality/ CV hospital admission	2	NS	NS	NS
MRA					
RALES[32]	All cause mortality	54	54	46	41
EMPHASIS-HF[33]	CV death/ HF hospitalisation	61	5	3	49
H-ISDN					
A-HeFT[34]	Composite score	-	3	2	15
Digoxin					
DIG[35]	All cause mortality	NS	NS	NS	191
Ivabradine					
SHIFT[36]	CV death/ HF hospitalisation	67	NS	NS	91
LCZ696					
PARADIGM-HF[37]	CV death/HF hospitalisation	118	49	66	54
ICD					
SCD-HeFT[38,39]	All cause mortality	22	22	11	-
CRT					
CARE-HF[40]	All cause mortality/ hospitalisation	40	15	8	37
RAFT[41]	All cause mortality/HF hospitalisation	23	12	0	24
LVAD					
REMATCH[42]	All cause mortality	10	10	-	-
Home Monitoring					
CHAMPION[16,43]	HF hospitalisations up to six months	-	NS	NS	4
IN-TIME[44]	Worse composite score	-	5	3	NS
Exercise Training					
HF-ACTION[45]	All cause mortality/ hospitalisation	0¶	NS	NS	-

* = Primary endpoint was all case mortality at 6 months follow up and number given for all cause mortality relates to number of deaths at the completion of the trial, ¶ = p <0.05 after adjustment, - = not reported.
Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; A-HeFT, African-American Heart Failure Trial; ARB, angiotensin receptor blocker; ATLAS, Assessment of Treatment with Lisinopril And Survival; CARE-HF, CArdiac REsynchronization in Heart Failure; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients; CHARM-Added, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Added; CHARM-Alternative, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity - Alternative; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; COMET, Carvedilol Or Metoprolol European Trial; CONSENSUS, COoperative North Scandinavian ENalapril SUrvival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; CRT, cardiac resynchronization therapy; CV, cardiovascular; DIG ,Digitalis Investigation Group; EMPHASIS–HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HEAAL, Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan study; HF, heart failure; HF-ACTION, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training;H-ISDN, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter defibrillator; IN-TIME, Influence of Home Monitoring on the Clinical Status of Heart Failure Patients; LVAD, left ventricular assist device; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure; MP, matching placebo; MRA, mineralocorticoid receptor antagonist; NS, not significant ($p \geq 0.05$); PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; RAFT, Resynchronization–defibrillation for Ambulatory heart Failure trial; RALES, Randomized Aldactone Evaluation Study; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; SHIFT, Systolic Heart failure treatment with the If inhibitor ivabradine Trial; SOLVD –Treatment, Studies of Left ventricular dysfunction- treatment; Val-HeFT, Valsartan Heart Failure Trial.

Table 4: Fragility index for the primary outcome at the statistical boundaries of p<0.05 and p<0.00125

Trial	Fragility Index	
	p<0.05	p<0.00125
ACE- i		
CONSENSUS	7	0
SOLVD Treatment	10	0
ARB		
Val-HeFT	17	0
CHARM Alternative	29	2
CHARM Added	8	0
HEAAL	4	0
^{2} -Blockers		
CIBIS II	37	14
MERIT HF	34	11
COPERNICUS	30	9
COMET	33	0
SENIORS	2	0
MRA		
RALES	54	29
EMPHASIS HF	61	33
Ivabradine		
SHIFT	67	22
LCZ696		
PARADIGM HF	118	68
ICD		
SCD-HeFT	22	0
CRT		
CARE HF	40	22
RAFT	23	0
LVAD		
REMATCH	10	3
Exercise Training		
HF-ACTION	0¶	0

¶ = p <0.05 after adjustment.
Abbreviations as in Table 3.

Supplementary Data

Table 1: Chronic heart failure randomised controlled trials included in analysis

Table 2: Fragility index of neutral trials

Figure 1: Fragility index calculation

Table 1: Chronic heart failure randomised controlled trials included in analysis

Trial	n	Follow up (months) Mean/ Median*	Treatment A (n)	Treatment B (n)	Primary Endpoint	Primary Endpoint A n (%)	Primary Endpoint B n (%)	All Cause Mortality A n (%)	All Cause Mortality B n (%)	CV Mortality A n (%)	CV Mortality B n (%)	HF Hospitalisation A n (%)	HF Hospitalisation B n (%)	LTFU A n (%)	LTFU B n (%)	Stopped Early
ACE-I																
CONSENSUS[1]	253	6.3	Enalapril (127)	MP (126)	All cause mortality at 6 months	33 (26)	55 (44)	50# (39)	68# (54)	49 (39)	68 (54)	-	-	0 (0.0)	0 (0.0)	Yes
SOLVD-Treatment[2]	2569	41.4	Enalapril (1285)	MP (1284)	All cause mortality	452 (35)	510 (40)	452 (35)	510 (40)	399 (31)	461 (36)	332 (26)	470 (37)	1 (0.1)	1 (0.1)	No
ATLAS[3,4]	3164	45.7*	High dose lisinopril (1568)	Low dose lisinopril (1596)	All cause mortality	666 (42)	714 (45)	666 (42)	714 (45)	583 (37)	641 (40)	526 (34)	611 (38)	0 (0.0)	0 (0.0)	No
ARB																
Val-HeFT[5,6]	5010	23	Valsartan (2511)	MP (2499)	All cause mortality/ HF hospitalisation/ resuscitated cardiac arrest/administration of IV inotropic or vasodilator drugs for 4 or more hours.	723 (29)	801 (32)	495 (20)	484 (19)	427 (17)	419 (17)	346 (14)	455 (18)	3 (0.1)	4 (0.1)	No
CHARM-Alternative[7]	2028	33.7*	Candesartan (1013)	MP (1015)	CV death/ HF hospitalisation	334 (33)	406 (40)	265 (26)	296 (29)	219 (22)	252 (25)	207 (20)	286 (28)	2 (0.2)	1 (0.1)	No
CHARM-Added[8]	2548	41*	Candesartan (1276)	MP (1272)	CV death/ HF hospitalisation	483 (38)	538 (42)	377 (30)	412 (32)	302 (24)	347 (27)	309 (24)	356 (28)	3 (0.2)	1 (0.1)	No
HEAAL[9]	3834	56.4*	High dose losartan (1921)	Low dose losartan (1913)	All cause mortality/HF hospitalisation	828 (43)	889 (46)	635 (33)	665 (35)	448 (23)	478 (25)	450 (23)	503 (26)	41 (2.1)	54 (2.8)	No
^{2} -Blockers																
CIBIS II[10]	2647	16	Bisoprolol (1327)	MP (1320)	All cause mortality	156 (12)	228 (17)	156 (12)	228 (17)	119 (9)	161 (12)	159 (12)	232 (18)	5 (0.4)	1 (0.1)	Yes
MERIT-HF[11,12]	3991	12	Metoprolol CR/XL (1990)	MP (2001)	All cause mortality	145 (7)	217 (11)	145 (7)	217 (11)	128 (6)	203 (10)	200 (10)	294 (15)	0 (0)	0 (0)	Yes
COPERNICUS [13,14]	2289	10.4	Carvedilol (1156)	MP (1133)	All cause mortality	130 (11)	190 (17)	130 (11)	190 (17)	116 (10)	166 (15)	198 (17)	268 (24)	0 (0)	0 (0)	Yes
COMET[15,16]	3029	58	Carvedilol (1511)	Metoprolol Tartrate (1518)	All cause mortality	512 (34)	600 (40)	512 (34)	600 (40)	438 (29)	534 (35)	473 (31)	481 (32)	13§ (0.9)	20§ (1.3)	No
SENIORS[17]	2128	21	Nebivilol (1067)	MP (1061)	All cause mortality/ CV hospital admission	332 (31)	375 (35)	169 (16)	192 (18)	123 (12)	145 (14)	145 (14)	144 (14)	16 (1.5)	21 (2.0)	No
MRA																
RALES[18]	1663	24	Spironolactone (822)	MP (841)	All cause mortality	284 (35)	386 (46)	284 (35)	386 (46)	246 (30)	338 (40)	215 (26)	300 (36)	0 (0)	0 (0)	Yes
EMPHASIS-HF[19]	2737	21*	Eplerenone (1364)	MP (1373)	CV death/ HF hospitalisation	249 (18)	356 (26)	171 (13)	213 (16)	147 (11)	185 (13)	164 (12)	253 (18)	17 (1.2)	15 (1.0)	Yes
H-ISDN																
A-HeFT[20]	1050	10	H-ISDN (518)	MP (532)	Composite score	-	-	32 (6)	54 (10)	26 (5)	45 (8)	85 (16)	130 (24)	0 (0)	0 (0)	Yes

Digoxin																	
DIG[21]	6800	37	Digoxin (3397)	MP (3403)	All cause mortality	1181 (35)	1194 (35)	1181 (35)	1194 (35)	1016 (30)	1004 (30)	910 (27)	1180 (35)	47 (1.4)	46 (1.4)	No
Ivabradine																	
SHIFT[22]	6505	22.9*	Ivabradine (3241)	MP (3264)	CV death/ HF hospitalisation	793 (24)	937 (29)	503 (16)	552 (17)	449 (14)	491 (15)	514 (16)	672 (21)	75§ (2.3)	59§ (1.8)	No
LCZ696																	
PARADIGM-HF[23]	8399	27*	LCZ696 (4187)	Enalapril (4212)	CV death/HF hospitalisation	914 (22)	1117 (27)	711 (17)	835 (20)	558 (13)	693 (16)	537 (13)	658 (16)	11 (0.3)	9 (0.2)	Yes
ICD																	
SCD-HeFT[24,25]	1676	45.5*	ICD (829)	UC (847)	All cause mortality	182 (22)	244 (29)	182 (22)	244 (29)	133 (16)	179 (21)	-	-	0 (0)	0 (0)	No
CRT																	
CARE-HF[26]	813	29.4	CRT (409)	UC (404)	All cause mortality/ hospitalisation	159 (39)	224 (55)	82 (20)	120 (30)	57 (14)	86 (21)	72 (18)	133 (33)	0 (0)	0 (0)	No
RAFT[27]	1798	40	CRT-D (894)	ICD (904)	All cause mortality/HF hospitalisation	297 (33)	364 (40)	186 (21)	236 (26)	130 (15)	162 (18)	174 (19)	236 (16)	10§ (0.6)	5§ (0.6)	No
LVAD																	
REMATCH[28]	129	-	LVAD (68)	UC (61)	All cause mortality	41 (60)	54 (89)	41 (60)	54 (89)	-	-	-	-	0 (0)	2§ (3.3)	No
Home Monitoring																	
CHAMPION[29,30]	550	15	Device On (270)	MP (280)	HF hospitalisations up to six months	83 (31)	120 (43)	47 (17)	52 (19)	40 (15)	39 (14)	54 (20)	80 (29)	3§ (1.1)	4§ (1.4)	No
IN-TIME[31]	664	335(A)/ 326(B) Days	Telemonitoring (333)	UC (331)	Worse composite score	63 (19)	90 (27)	10 (3)	27 (8)	8 (2)	21 (6)	27 (8)	34 (10)	10§ (3.0)	13§ (13.9)	No
Exercise Training																	
HF-ACTION[32]	2331	30*	Exercise Training (1159)	UC (1172)	All cause mortality/ hospitalisation	759 (65)	796 (68)	189 (16)	198 (17)	131 (11)	143 (12)	-	-	59§ (5.1)	63§ (5.4)	No

*= Median, # = All cause mortality at end of trial follow up § = Includes withdrawal of consent, ¶ = p <0.05 after adjustment, - = not reported

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; A-HeFT, African-American HEart Failure Trial; ARB, angiotensin receptor blocker; ATLAS, Assessment of Treatment with Lisinopril And Survival; CARE-HF, CArdiac REsynchronization in Heart Failure; CHAMPION, CardioMEMS Heart sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients; CHARM-Added, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Added; CHARM-Alternative, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity - Alternative; CIBIS II, Cardiac Insufficiency BIsoprolol Study II; COMET, Carvedilol Or Metoprolol European Trial; CONSENSUS, COoperative North Scandinavian ENalapril SUrvival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; CRT, cardiac resynchronization therapy; CV, cardiovascular; DIG, Digitalis Investigation Group; EMPHASIS–HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HEAAL, Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan study; HF, heart failure; HF-ACTION, Heart Failure: A Controlled Trial Investigating Outcomes of exercise traiNing;H-ISDN, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter defibrillator; IN-TIME, Influence of Home Monitoring on the Clinical Status of Heart Failure Patients; LTFU, lost to follow up; LVAD, left ventricular assist device; MERIT-HF, MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure; MP; matching placebo; MRA; mineralocorticoid receptor antagonist; PARADIGM-HF; Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; RAFT, Resynchronization–defibrillation for Ambulatory heart Failure Trial; RALES, Randomized Aldactone Evaluation Study; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; SHIFT, Systolic Heart failure treatment with the If inhibitor ivabradine Trial; SOLVD –Treatment, Studies Of Left Ventricular Dysfunction- treatment; UC, usual care; Val-HeFT, VALsartan Heart Failure Trial.

Table 2: Fragility index of neutral trials

Trial	n	Treatment A (n)	Treatment B (n)	Primary Outcome	Event treatment A n (%)	Event treatment B n (%)	Stopped early	Fragility index
STICH[33]	1212	UC + CABG (610)	UC (602)	All cause mortality	218 (36)	244 (41)	No	5
OVERTURE[34]	5770	Omapatrilat (2886)	Enalapril (2884)	All cause mortality/HF hospitalisation	914 (32)	973 (34)	No	11
BEST[35]	2708	Bucindolol (1354)	MP (1354)	All cause mortality	411 (30)	449 (33)	No	11
STAT-CHF[36]	674	Amiodarone (336)	MP (338)	All cause mortality	131 (39)	143 (42)	No	14
PRAISE I[37]	1153	Amlodipine (571)	MP (582)	All cause mortality/CV hospitalisation	222 (39)	246 (42)	No	14
ACCLAIM[38]	2426	Immunomodulation (1213)	MP (1213)	All cause mortality/CV hospitalisation	399 (33)	429 (35)	No	17
CORONA[39]	5011	Rosuvastatin (2514)	MP (2497)	CV death/MI/Stroke	692 (28)	732 (29)	No	19
ATMOSPHERE[40]	4676	Aliskiren + Enalapril (2340)	Enalapril (2336)	CV death/ HF hospitalisation	770 (33)	808 (35)	No	25
ANDROMEDA[41]	627	Dronederone (310)	MP (317)	All cause mortality/ HF hospitalisation	53 (17)	40 (12)	Yes	29
DIAMOND-HF[42]	1518	Dofetilide (762)	MP (756)	All cause mortality	311 (41)	317 (42)	No	30
WARCEF[43]	2305	Warfarin (1142)	Aspirin (1163)	All cause mortality/ Ischaemic stroke/ICH	302 (26)	320 (28)	No	30
ESSENTIAL[44]	1854	Enoximone (926)	MP (928)	All cause mortality/CV hospitalisation	458 (49)	465(50)	No	37
ECHO-CRT[45]	809	CRT on (404)	CRT off (405)	All cause Mortality/ HF hospitalisation	116 (29)	102 (25)	Yes	39
AF-CHF[46]	1376	Rhythm Control (682)	Rate Control (694)	CV Death	182 (27)	175 (25)	No	41
FIRST[47]	471	Epoprostenol (237)	UC (234)	All cause mortality	114 (48)	87 (37)	Yes	47
PRAISE II[48]	1654	Amlodipine (827)	MP (827)	All Cause Mortality	278 (34)	262 (32)	No	54
ECHOS[49]	1000	Nolomirole (501)	MP (499)	All cause mortality/ HF Hospitalisation	233 (47)	208 (42)	No	56
RED-HF[50]	2278	Darbopoetin (1136)	MP (1142)	All cause mortality/ HF Hospitalisation	576 (51)	565 (49)	No	61
MACH I[51]	2590	Mibefradil (1295)	MP (1295)	All cause mortality	350 (27)	319 (25)	No	74
GISSI-HF Rousvastatin[52]	4574	Rosuvastatin (2285)	MP (2289)	All cause mortality	657 (29)	644 (28)	No	74

Abbreviations; ACCLAIM, Advanced Chronic heart failure CLinical Assessment of IMmunomodulation; AF-CHF, Atrial Fibrillation and Congestive Heart Failure; ANDROMEDA, ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse; ATMOSPHERE, The Aliskiren Trial to Minimize OutcomeS in Patients with HEart FailuRE; BEST, Beta-blocker Evaluation of Survival Trial; CORONA, COntrolled ROsuvastatin multiNAtional Trial in Heart Failure; CRT, Cardiac Resynchronization Therapy; CV, CardioVascular; DIAMOND–HF, Danish Investigations of Arrhythmia and Mortality ON Dofetilide; ECHO-CRT, ECHOcardiography guided Cardiac Resynchronization Therapy; ECHOS, EchoCardiography and Heart Outcome Study; ESSENTIAL, The Studies of Oral Enoximone Therapy in Advanced Heart Failure; FIRST, The Flolan International Randomized Survival Trial; GISSI-HF rosuvastatin, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca Heart Failure trial rosuvastatin; HF, Heart Failure; ICH, IntraCranial Haemorrhage; MACH I, Mortality Assessment in Congestive Heart Failure Trial; MOXCON, MOXonidine CONgestive heart failure trial; MP, Matching Placebo; OVERTURE, the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; PRAISE I, Prospective Randomized Amlodipine Survival Evaluation; PRAISE II, Prospective Randomized Amlodipine Survival Evaluation II; PRIME II, Prospective Randomised study of Ibopamine on Mortality and Efficacy II; RED-HF, Reduction of Events by Darbepoetin alfa in heart failure; SERVE-HF, Adaptive SERvo-VEntilation for central sleep apnea in systolic Heart Failure; STAT-CHF, Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure; STICH, Surgical Treatment for Ischemic Heart Failure; UC, Usual Care; WARCEF, Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction.

Figure 1

Trial Result		
	Event	No Event
Treatment A (Investigational)	a	b
Treatment B (Comparator)	c	d
Fisher's Exact Test $p<0.05$		

Fragility Index Calculation		
	Event	No Event
Treatment A (Investigational)	a + f	b - f
Treatment B (Comparator)	c	d
Fisher's Exact Test $p\geq0.05$		

Fragility index calculation – One event at a time is iteratively added to the group with smaller number of events (while subtracting one patient from the group with no events to maintain the total number of patients constant). The smallest number of events, "f", resulting in a Fisher's exact p-value ≥0.05 is the fragility index. Trials with a higher fragility index are more robust.

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